CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
PYRACLOSTROBIN

Chemical Code # 5759, Tolerance # 52851
SB 950 # N/A
Original: 1/3/01
Revised: 6/5/01

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time[1]

Toxicology one-liners are attached.

All studies through record number 180452 were examined (Document No. 52851-098).
In the one-liners below:

** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T183369 S00.doc

[1] Acceptable acute and subchronic rat neurotoxicity studies were submitted and no adverse effects

were noted.

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

(See separate entries under rat chronic and rat oncogenicity)

CHRONIC TOXICITY, RAT

**52851-026 175065 Mellert, W., K. Deckardt, C. Gembardt, G. Pappritz, and B. Hildebrand, "BAS 500 F – Chronic toxicity study in Wistar rats administration in the diet for 24 months," BASF AG, Ludwigshafen, 11/09/99. Lab Project ID 82S0494/96085. Twenty rats/sex/group were dosed in diet with Pyraclostrobin (BAS 500 F) [97.09% purity] at 0, 25, 75, or 200 ppm in a standard chronic study. NOEL = 75 ppm (3.4 and 4.6 mg/kg/day in M and F, respectively), based on slight body weight decrements and on reductions in activities of circulating enzymes [alanine aminotransferase (M) and alkaline phosphatase (M and F)] at 200 ppm. The latter observations may reflect a change in liver functional state, consistent with evidence of liver as a target organ at 500 ppm and above in the 3-month dietary study in Wistar rats (Mellert et al., 1999: DPR Record No. 175050). Acceptable, with no adverse effects. Aldous, 01/02/01.

CHRONIC TOXICITY, DOG

** 52851-025, 098; 175059, 180451; Schilling, K., K. Deckardt, C. Gembardt, and B. Hildebrand, "BAS 500 F – Chronic oral toxicity study in beagle dogs administration in the diet for 12 months," BASF AG, Ludwigshafen, 11/17/99. Report No. 33D0494/96144. Dogs received pyraclostrobin ("BAS 500 F", 98.7% purity) in diet at 0, 100, 200, or 400 ppm (5/sex/group) in a standard chronic study. Chronic NOEL = 200 ppm, equivalent to 5.4 mg/kg/day in M and F. LOEL's in M and F were 10.8 and 11.2 mg/kg/day. Both sexes at 400 ppm suffered from diarrhea throughout much of the study. High dose females consumed less diet and gained appreciably less weight than other groups. Both sexes had reduced levels of circulating cholesterol. Very modest but typically consistent reductions in circulating total protein and of the associated albumin and globulin fractions at 400 ppm were also plausibly treatment effects. Hematology observations, particularly equivocal elevations in platelet counts, may have been treatment-related. There were no gross nor microscopic changes at necropsy. Study upgraded to **acceptable**; **No adverse effects**; (Aldous, 12/11/00; upgraded, Leung, 6/1/01)

ONCOGENICITY, RAT

**52851-028 175073 Mellert, W., K. Deckardt, C. Gembardt, G. Pappritz, and B. Hildebrand, "BAS 500 F – Carcinogenicity study in Wistar rats administration in the diet for 24 months," BASF

AG, Ludwigshafen, 11/22/99. Report No. 82S0494/96086. Fifty rats/sex/group were dosed in diet with Pyraclostrobin (BAS 500 F) [97.09% purity] at 0, 25, 75, or 200 ppm in a standard oncogenicity study. NOEL = 75 ppm (3.4 and 4.7 mg/kg/day in M and F, respectively), based primarily on body weight decrements at 200 ppm. Hepatocellular necrosis in 200 ppm males was also plausibly treatment-related, consistent with liver responses previously observed in the associated subchronic study (DPR Record No. 175050). **Acceptable** to evaluate oncogenicity effects. **No adverse effects**. Aldous, 01/03/01.

ONCOGENICITY, MOUSE

52851-027 175069 Mellert, W., K. Deckardt, K. Küttler, and B. Hildebrand, "BAS 500 F – Carcinogenicity study in B6C3F1 mice administration in the diet for 18 months," BASF AG, Ludwigshafen, 11/22/99. Laboratory Project No. 76C0494/96101. Fifty mice/sex/group were dosed in diet with 0, 10, 30, 120, or 180 (females only at this dose) ppm pyraclostrobin (97.09% purity) for 18 months in a standard oncogenicity study. **The overall NOEL for females cannot be determined from available information due to uncertainties about hematology data interpretation: circulating monoblasts were seen in seven 180 ppm females at 1.5 years, vs. none in other groups or time periods examined. Intermediate groups were not examined for hematology. The most definitive treatment effect was body weight decrement in 120 ppm males and 180 ppm females [hence apparent NOEL **for body weight reduction** = 4.1 mg/kg/day (M) and 20.5 mg/kg/day (F)]. The study is **acceptable for oncogenicity assessment**. Information is requested concerning above hematology issues in females. In particular, blood smear data are requested on intermediate groups of females, if available. The registrant may additionally elect to send laboratory historical control blood smear data for perspective on this parameter. There was no oncogenicity under test conditions. The possible hematology effect noted in this review does not warrant special "adverse" effect designation at this time. The information requested on blood smears of intermediate groups of females is primarily for completeness. Aldous, 1/03/01.

REPRODUCTION, RAT

**52851-024 175058 Schilling, K., C. Gembardt, and B. Hildebrand, "BAS 500 F – Two generation reproduction study in Wistar rats continuous dietary administration," BASF AG, Ludwigshafen, 11/29/99. Lab Project ID # 70R0494/96172. Twenty-five rats/group/generation were dosed continuously in diet with 0, 25, 75, or 300 ppm pyraclostrobin (98.7%) in a standard reproduction study with 1 littering period/generation. Estrous cycle data were collected on dams beginning 3 weeks prior to mating. Pup sexual development was evaluated via time to vaginal opening (F) or preputial separation (M). Necropsies of males included examinations of sperm motility, morphology, and head count. Necropsies of females included serial sections of ovaries to permit evaluations of numbers of primordial follicles, growing follicles, antral follicles, and corpora lutea. Systemic NOEL = 75 ppm (7.4 and 7.8 mg/kg/day for F0 males and females, respectively). Adults showed modest body weight and food consumption decrements, and a reduction in incidence or degree of liver microscopy observations of fatty infiltration at the acinar periphery (particularly in females). Reproductive NOEL = 300 ppm (no effects at HTD). Developmental NOEL = 75 ppm. Pup body weight gain was significantly reduced in both generations. Vaginal opening was delayed significantly in

females. A small but statistically significant decrement in brain weights of F2 weanlings was consistent with growth delays. Decrements in F1 and F2 weanling thymus and spleen weights were significant, but organ weight decrements did not carry on as F1 rats matured. **Acceptable, with no adverse effects**: findings in offspring were not of any type, degree, or persistence which is of toxicological concern. Aldous, 01/02/01.

TERATOLOGY, RAT

52851-022 175054 Schilling, K., J. Hellwig, and B. Hildebrand, "BAS 500 F – Prenatal developmental toxicity study in Wistar rats oral administration (gavage)," BASF AG, Ludwigshafen, 10/25/99. Project ID No. 30R0494/96168. Rats were dosed daily by gavage on pc days 6-19 with 0, 10, 25, or 50 mg/kg/day pyraclostrobin (98.9% purity) in aqueous 0.5% Tylose CB 30.000 suspension (sacrifice on day 20) in a standard developmental toxicity study, 25/group. Food consumption was reduced in 25-50 mg/kg/day groups, particularly during the first 2 days of treatment. Thus maternal NOEL = 10 mg/kg/day (dose-related decline in food consumption). Maternal body weight gain was statistically significantly reduced at 50 mg/kg/day. Developmental NOEL = 25 mg/kg/day (increased incidence of cervical ribs). **Acceptable with no adverse effects. Aldous, 01/02/01.

TERATOLOGY, RABBIT

52851-023 175055 Schilling, K., J. Hellwig, and B. Hildebrand, "BAS 500 F – Prenatal developmental toxicity study in Himalayan rabbits oral administration (gavage)," BASF AG, Ludwigshafen, 10/25/99. Report # 40R0494/96159. Twenty-five artificially inseminated does per group received 0, 5, 10, or 20 mg/kg/day pyraclostrobin (98.9% purity) on days 7-28 in a standard developmental toxicity study. Maternal NOEL is less than 5 mg/kg/day, based on transiently reduced food consumption and body weight. Food consumption reductions were substantial, longer in duration, and dose-related at higher treatment levels. Associated clinical signs of "reduced defecation" were noted for 1 mid-dose doe and 10 high-dose does. Developmental effects NOEL = 5 mg/kg/day, based on dose-related early resorptions, leading to whole litter losses of 2 and 3 litters at 10 and 20 mg/kg/day, respectively. These cases were associated with signs of "blood in bedding." There was a reduction in live litter sizes at 20 mg/kg/day, due to a substantial increase in early resorptions among does having viable fetuses at term. There were no reductions in fetal weights in any groups. There were no treatment-related malformations or variations (including delayed development). **Acceptable, with no adverse effect (developmental toxicity was only evident at doses which elicited marked maternal toxicity or major nutritional disturbances in the does). Aldous, 12/29/00.

GENE MUTATION

**52851-029 175078 Engelhardt, G., "BAS 500 F – (Reg. No. 304 428) (ZHT Test Substance No.: 96/308) in the Ames Salmonella/mammalian-microsome mutagenicity test and Escherichia coli/mammalian-microsome reverse mutation assay (standard plate test and preincubation test)," BASF AG, Ludwigshafen, 7/31/97. Sponsor Report No. 1997/10973. Bacterial strains TA 1535, TA 100,

TA 1537, TA 98 and E. coli WP2 uvrA were evaluated in standard plate tests and in preincubation tests (20 min) at dose levels of 0, 20, 100, 500, 2500, and 5000 µg/plate of BAS 500 F [pyraclostrobin, purity 98.2%]. Treatments were with and without S9 activation, 3 reps per treatment/strain/method combination, and there were no repeat assays. Treatments did not affect cell viability. Precipitate was observed at 2500 µg/plate and above. All pyraclostrobin treatment responses were negative, and all positive controls were functional. The study is **acceptable, with no adverse effects**. Aldous, 01/02/01.

52851-029 175084 Engelhardt, G., "In vitro gene mutation test with BAS 500 in CHO cells (HPRT locus assay)," BASF AG, Ludwigshafen, 12/8/98. Sponsor Report No. 1998/11422. BAS 500 F (pyraclostrobin), purity 98.2%, was administered to CHO K1 cells at dose levels of 0 [untreated], 0 [with DMSO vehicle], 0.625, 1.25, 2.5, 5.0, 10.0, and 20.0 µg/ml. Positive controls for tests without or with S9 (EMS and 3-MCA, respectively) were included. This design constituted Experiment 1 (same dose sequence both with and without S9). Each dose/treatment combination represented two independent treated populations, subsamples of which were distributed to 6 flasks each for assessment of mutation frequencies. A response at 5 µg/ml (without S9) achieved the criterion for an apparent treatment effect. Therefore a second experiment was undertaken without S9 at dose levels of 3, 4, 5, 6, 7, and 8 µg/ml. This experiment did not reproduce the response. Repeat tests with and without S9 were undertaken over dose ranges of 1.25 to 20 µg/ml (Experiment 3), with no treatment effects. Positive controls were functional. Study is **acceptable, and **does not indicate an adverse effect**. Aldous, 01/02/01.

CHROMOSOME EFFECTS

52851-029 175080 Engelhardt, G., "In vitro chromosomal aberration assay with BAS 500 F in V79 cells," BASF AG, Ludwigshafen, 10/8/99. Sponsor Report No. 1999/11403. Chinese hamster-derived V79 cell line cultures were exposed either with or without S9 for 4 hr to pyraclostrobin (purity 98.2%) at levels of 0, 6.25, 12.5, or 25 µg/ml, followed by 14 hr incubation without further exposure. Functional positive controls were ethyl methane sulfonate (w/o S9) or cyclophosphamide (with S9). A continuous exposure study without S9 utilized much lower dose levels (0.005 to 0.10 µg/ml) for 18 hr. Finally, an additional study with S9 involved a 4 hr exposure period to 0, 3.125, 6.25, or 12.5 µg/ml pyraclostrobin, with cyclophosphamide positive controls, but having a 24-hr incubation time after exposure. Assayed pyraclostrobin levels were justifiable based on cytotoxicity studies. No pyraclostrobin results were outside historical control range, nor were there reproducible indications of treatment response. Study is **acceptable, with no adverse effect. Aldous, 12/8/00.

**52851-029 175082 Engelhardt, G., "Cytogenetic study in vivo with BAS 500 F in the mouse micronucleus test single oral administration," BASF AG, Ludwigshafen, April 9, 1998. Sponsor Report No. 1998/10460. Five NMRI mice/sex were dosed once with 0 (olive oil), 75, 150, or 300 mg/kg pyraclostrobin (BAS 500 F, purity 98.2%) by gavage 24 hr before sacrifice. An additional 5 mice/sex were dosed 48 hr before sacrifice with 0 or 300 mg/kg pyraclostrobin. Positive controls (20 mg/kg cyclophosphamide and 0.15 mg/kg vincristine) were administered to 2-3 mice/sex 24 hr before sacrifice to evaluate clastogenicity or spindle effects, respectively. Femoral bone marrow smears were prepared, stained, and examined for micronuclei (2000 PCE's per mouse). Clinical signs (piloerection and

squatting position) were seen at all dose levels at about 30 min after treatment. Pyraclostrobin did not elicit micronuclei, whereas positive controls were functional. **Acceptable, with no adverse effect**. Aldous, 01/02/01.

DNA DAMAGE

52851-029 175085 Engelhardt, G., "In vitro unscheduled DNA Synthesis (UDS) assay with BAS 500 F in primary rat hepatocytes," BASF AG, Ludwigshafen, 10/19/98. Sponsor Report No. 1998/11421. Primary hepatocyte cultures were obtained from male Wistar rats following perfusion, collagenase treatment, and distribution to wells with coverslips in attachment medium. Cytotoxicity studies had shown that LDH levels rose rapidly with dose in the range from 0 to 1 µg/ml. Lactate concentrations were decreased over the same range. Morphological changes in cells at 1 µg/ml were observed in experiment #1 of the UDS study. UDS experiment examined 100 readable cells per dose. The first experiment evaluated untreated controls, DMSO controls, and pyraclostrobin at 0.01, 0.03, 0.1, 0.3, and 1.0 µg/ml, with positive control (2-AAF) at 4.0 µg/ml for 18-20 hours in the presence of ^{3}H-thymidine. A second experiment was of similar design, with pyraclostrobin dose levels of 0.004, 0.02, 0.1, and 0.5 µg/ml. Net nuclear grain counts in all pyraclostrobin groups were similar to controls, whereas the positive controls were clearly effective. Study is **acceptable, with no adverse effect. Aldous, 01/02/01.

NEUROTOXICITY

030; 175087; "BAS 500 F-Acute Oral Neurotoxicity Study in Wistar Rats" (Mellert, W. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 20C0494/96164, Sponsor Report # 1999/11111, 8/18/99). 818. BAS 500 F (Batch: LJ.-No.28632/147FS; CP 029053, purity=99.0%), suspended in a 0.5% aqueous solution of carboxymethylcellulose, was administered by gavage in a single dose to 10 Wistar rats per sex per dose at dose levels of 0 (vehicle only), 100, 300, and 1000 mg/kg. No mortalities occurred. Treatment-related soft feces and/or diarrhea were observed in males at 100, 300, and 1000 mg/kg on Day 0 (within a few hours after dosing). Treatment-related diarrhea and piloerection were observed in females on Day 0. No treatment-related effects were observed during FOB assessments conducted on days 7 and 14. Motor activity assessments revealed no treatment-related effects in the mean total number of beam interrupts. Neuropathological examination revealed no treatment-related abnormalities. **No adverse effects**. NOEL (M)< 100 mg/kg (based on treatment-related soft feces/diarrhea); NOEL (F)=300 mg/kg (based on treatment-related diarrhea and piloerection). **Acceptable**. (Corlett and Leung, 11/2/00)

031; 175089; "BAS 500 F-Subchronic Oral Neurotoxicity Study in Wistar Rats Administration in the Diet for 3 Months" (Mellert, W. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 50C0494/96174, Sponsor Report # 1999/11329, 9/16/99). BAS 500 F (Batch: LJ.-No. 27 882/191/c; (Tox.III/Part 1), purity=97.09%) was admixed to the diet at dose levels of 0 (ground diet only), 50, 250, 750 (males only), or 1500 (females only) ppm (for males, 0, 3.5, 16.9, and 49.9 mg/kg/day, respectively, and for females, 0, 4.0, 20.4, and 111.9 mg/kg/day, respectively) and fed to 10 Wistar rats per sex per dose daily for 3 months. No animals died. No clinical signs were observed. A treatment-related decrease in mean body weight was

observed in males at 750 ppm. Treatment-related decreases in mean food (in males at 250 and 750 ppm and in females at 1500 ppm) and mean water (in males at 750 ppm and in females at 1500 ppm) consumption were observed. FOB assessments revealed no treatment-related effects other than a treatment-related decrease in mean forelimb grip strength on Day 85 in females at 1500 ppm. Motor activity assessments revealed no treatment-related overall motor activity effects. Macroscopic and microscopic examinations revealed no treatment-related effects. **No adverse effects**. NOEL (M)= 3.5 mg/kg/day (50 ppm) decreased food consumption and NOEL (F)=20.4 mg/kg/day (250 ppm) based on decreased food and water consumption and decreased forelimb strength. **Acceptable**. (Corlett, 11/30/00)

METABOLISM

52851-033 175092 Leibold, E., H. Hoffmann, and B. Hildebrand, "BAS 500 F – Study of the biokinetics in rats," BASF AG, Ludwigshafen, Oct. 1, 1998. Report No. 02B0364/966007. Wistar rats were dosed with chlorophenyl-labeled pyraclostrobin (>98% chemical purity, >98% radiochemical purity) or tolyl-labeled pyraclostrobin (>98% chemical purity, >98% radiochemical purity), adjusted with unlabeled pyraclostrobin (BAS 500 F), 99.8 % purity to desired dose, to assess biokinetic parameters. Single doses of 5 or 50 mg/kg pyraclostrobin were administered in 0.5% aqueous Tylose suspensions to small groups of male and female rats. The majority of tests were done with tolyl-labeled a.i., however sufficient testing was done with chlorophenyl-labeled pyraclostrobin to determine that there were no noteworthy differences between the two labeled materials. Some rats were pre-treated with unlabeled pyraclostrobin (50 mg/kg/day for 2 weeks) prior to a single treatment with 5 mg/kg/day tolyl-labeled pyraclostrobin. RESULTS: There was no exhaled ^{14}C-$C0_2$ detected. There was little difference in disposition patterns regardless of dose, sex, label position, or pre-treatment with unlabeled pyraclostrobin prior to treatment with labeled pyraclostrobin. About one-third of administered dose was excreted in bile. About one-half of the dose was not absorbed, based on approximately 80% of residues being eliminated in feces, of which less than 50% was biliary contribution. Urinary excretion was about 10 to 15% of dose. Study did not show tissue bio-accumulation. Terminal plasma half-life estimates (with peak levels usually appearing from 8 to 24 hr after dosing) ranged from 20-37 hr. Study provides valid absorption, distribution, and elimination patterns data, complementary to the metabolite analysis of Record No. 175093. Aldous, 11/29/00.

**52851-033 175093 Velic, I., "Metabolism of ^{14}C-BAS (^{14}C-304428) in rats," BASF AG, Limburgerhof, Germany, Dec. 1, 1999. Sponsor Report No. 1999/11781. Wistar rats were dosed in Record No. 175092 with chlorophenyl-labeled pyraclostrobin (>98% chemical purity, >98% radiochemical purity) or tolyl-labeled pyraclostrobin (>98% chemical purity, >98% radiochemical purity), adjusted with unlabeled pyraclostrobin (BAS 500 F), 99.8 % purity to desired dose. Tissues and excreta from that study were supplemented by additional samples provided at the Limburgerhof facility under comparable conditions to evaluate metabolite profiles. Tissue samples were collected 8 hr after dosing, to achieve maximal tissue levels for analysis. Data did not demonstrate sex differences. Dose levels (5 or 50 mg/kg) and treatment history (2 week pre-treatment with 50 mg/kg/day pyraclostrobin) had no apparent effect on metabolic disposition. The most abundant fecal metabolite was 500M08 (de-methoxylated a.i., which is hydroxylated in the 4-position of the pyrazole ring), accounting for about 38% of total administered dose. Other significant fecal metabolites were further hydroxylated: usually on the chlorophenyl ring and sometimes also on the tolyl ring. The major biliary

metabolite was 500M46 (formed by hydroxylation followed by glucuronidation of carbon 4 of the pyrazole group of the a.i.). The majority of lesser biliary metabolites were also glucuronides. No single urinary metabolite comprised more than about 3% of administered dose. Predominant urinary metabolites were various products of cleavage of the ether oxygen (often to form a glucuronide or benzoic acid derivative), or 500M06 (de-methoxylated 500M46). Detectable plasma residues were limited to 500M06 and 500M46 (representing about 0.02% of administered dose). These metabolites plus parent pyraclostrobin were found in liver in higher amounts (these 3 residues combined representing about 0.5% of dose). Only pyraclostrobin could be detected in kidneys, to the extent of about 0.03% of dose. Thus absorbed pyraclostrobin is efficiently metabolized to polar products and is cleared effectively from the body. **The two records in this document address the metabolism data requirements, with no adverse effect**. Aldous, 11/30/00.

SUBCHRONIC STUDIES

(Oral)

018; 175050; "BAS 500 F-Subchronic Oral Toxicity Study in Wistar Rats Administration in the Diet for 3 Months" (Mellert, W. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 50C0183/96015, Sponsor Report # 1999/10195, 7/2/99). BAS 500 F (Batch No. CP 025394, purity=98.4%) was admixed to the diet at dose levels of 0 (diet only), 50, 150, 500, 1000, or 1500 ppm (for males, 0, 3.5, 10.7, 34.7, 68.8, and 105.8 mg/kg/day, respectively, and for females, 0, 4.2, 12.6, 40.8, 79.7, and 118.9 mg/kg/day, respectively) and fed to 10 Wistar rats per sex per dose for 3 months. No animals died. No clinical signs were observed. In females, treatment-related decreases in mean red blood cell and hemoglobin (at 1000 and 1500 ppm) and mean hematocrit (at 1500 ppm) levels were observed. A treatment-related increase in mean reticulocyte levels in males at 1000 and 1500 ppm and in females at 1500 ppm was observed. A treatment-related increase in total bilirubin levels in males at 1000 and 1500 ppm and in females at 1500 ppm was observed. Treatment-related increases in mean relative liver and spleen weights (in males beginning at 1000 ppm and in females beginning at 500 ppm) were observed. Microscopic examination revealed treatment-related hepatocellular hypertrophy (in males beginning at 500 ppm and in females at 1500 ppm), extramedullary hematopoiesis in the spleen (in females beginning at 150 ppm), histiocytosis (in both sexes beginning at 150 ppm) and distension of sinusoids in the spleen (in both sexes beginning at 500 ppm) and hyperplasia of the mucosa of the duodenum (in males beginning at 500 ppm and in females at 1500 ppm). **No adverse effects**. NOEL (M)=3.5 mg/kg/day (50 ppm) and NOEL (F)=4.2 mg/kg/day (50 ppm) based on microscopic findings in the spleen (histiocytosis (both sexes) and extramedullary hematopoiesis (females)). **Acceptable**. (Corlett, 11/21/00)

019; 175051; "BAS 500 F-Repeated Dose Oral Toxicity Study in Wistar Rats Administration in the Diet for 4 Weeks" (Mellert, W. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 30C0376/95083, Sponsor Report # 1999/11870, 12/2/99). BAS 500 F (Batch-/Lab.-Journal Nos. 27 882/37/a and 27 655/160 with purities of about 94% and about 99%, respectively), was admixed to the diet at dose levels of 0 (diet only), 20, 100, 500, or 1500 ppm (for males, 0, 1.8, 9.0, 42.3, and 120.2 mg/kg/day, respectively, and for females, 0, 2.0, 9.6, 46.6, and 126.3 mg/kg/day, respectively) and fed to 5 Wistar rats per sex per dose for 4 weeks. No animals died. No clinical signs were observed. A statistically significant increase in

prothrombin time was observed at 500 and 1500 ppm in males and at 1500 ppm in females. Treatment-related increases in mean relative liver (in both sexes at 1500 ppm), spleen (in males at 1500 ppm and in females at 500 and 1500 ppm), and testes (at 500 and 1500 ppm) weight were observed. Microscopic examination revealed treatment-related decreased fat storage in the liver, extramedullary hematopoiesis in the spleen, and hyperplasia of the mucosa of the duodenum in both sexes at 500 and 1500 ppm. **No adverse effects**. NOEL (M)=9.0 mg/kg/day (100 ppm) and NOEL (F)=9.6 mg/kg/day (100 ppm) based on increased mean relative organ weights and microscopic findings. **Supplemental** (animals tested for only 4 weeks and only 5 animals per sex per dose used). (Corlett, 11/13/00)

020; 175052; "BAS 500 F-Subchronic Oral Toxicity Study in Beagle Dogs Administration in the Diet for 3 Months" (Menges, S. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 31D0494/96089, Sponsor Report # 1999/11678, 11/17/99). BAS 500 F (Batch No. LJ.-No. 27882/191/c (Tox. III, part 1), purity=97.09%) was admixed to the diet at dose levels of 0, 100, 200, or 450 ppm (for males, 0, 2.8, 5.8, and 12.9 mg/kg/day, respectively, and for females, 0, 3.0, 6.2, and 13.6 mg/kg/day, respectively) and fed to 5 beagle dogs per sex per dose daily for 3 months. No animals died. Treatment-related diarrhea was observed in males at 450 ppm and in females at 200 and 450 ppm. In females, a treatment-related decrease in mean body weight gain was observed at 450 ppm. A statistically significant increase in the mean platelet level in females at 450 ppm on Day 90 was observed. A treatment-related decrease in serum glucose levels in females at 200 and 450 ppm on Days 43 and 90 was observed. Macroscopic examination revealed slight thickening of the duodenal wall in both sexes at 450 ppm. Microscopic examination revealed mucosal hypertrophy in the duodenum in both sexes at 450 ppm. **No adverse effects**. NOEL (M)=5.8 mg/kg/day (200 ppm) based microscopic findings and incidences of diarrhea and NOEL (F)=3.0 mg/kg/day (100 ppm) based on incidences of diarrhea. **Acceptable**. (Corlett, 12/20/00)

017; 175048; "BAS 500 F-Subchronic Oral Toxicity Study in B6C3F1 crl BR Mice Administration in the Diet for 3 Months" (Mellert, W. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 60C0183/96016, Sponsor Report # 1998/11345, 11/25/99). BAS 500 F (Batch No. CP 025394, purity=98.5%) was admixed to the diet at dose levels of 0 (ground diet only), 50, 150, 500, 1000, or 1500 ppm (for males, 0, 9.2, 30.4, 119.4, 274.4, and 475.5 mg/kg/day, respectively, and for females, 0, 12.9, 40.4, 162.0, 374.1, and 634.8 mg/kg/day, respectively) and fed to 10 B6C3F1 Crl BR mice per sex per dose daily for 3 months. No treatment-related abnormalities occurred. No clinical signs were observed. A treatment-related decrease in mean body weight was observed in males beginning at 150 ppm and in females beginning at 500 ppm. A treatment-related increase in the serum urea levels beginning in males at 50 ppm and in females at 150 ppm was observed. Microscopic examination revealed treatment-related erosions or ulcers in the glandular stomach in males beginning at 500 ppm and in females beginning at 50 ppm, a treatment-related increase in thickening (in mm) of the duodenal mucosa in males beginning at 500 ppm and in females beginning at 150 ppm, and a treatment-related decrease in lipid vacuolization of cells of X-zone in the adrenal cortex in females beginning at 50 ppm. **No adverse effects**. NOEL (M)< 9.2 mg/kg/day (50 ppm) based on increased serum urea levels and NOEL (F)< 12.9 mg/kg/day (50 ppm) based on erosion or ulcers in the glandular stomach and decrease in lipid vacuolization in the adrenal cortex. **Supplemental** study (no ophthalmologic examinations were performed on the animals). (Corlett, 12/8/00)

(Dermal)

021; 175053; "BAS 500 F-Repeated Dose Dermal Toxicity Study in Wistar Rats Administration for 4 Weeks" (Mellert, W. et al., Department of Toxicology of BASF Aktiengesellschaft, Rhein, Germany, Laboratory Project Identification No. 33S0494/96179, Sponsor Report # 1999/11458, 10/15/99). 822. BAS 500 F (Batch No. LJ.-No. 28632/147FS CP 029053, purity=99%) was suspended in 0.5% carboxymethyl cellulose in twice distilled water and administered to the clipped skin of 10 Wistar rats per sex per dose at dose levels of 0 (vehicle control), 40, 100, or 250 mg/kg/day for 6 hours per day, 5 days per week for 4 weeks using a semi-occlusive dressing. No animals died. No signs of systemic toxicity were observed. No treatment-related body weight, hematological, or serum chemistry effects were observed. Microscopic examination revealed treatment-related hyperkeratosis of the treated skin in both sexes at 100 and 250 mg/kg/day and treatment-related epidermal thickening of the treated skin in both sexes at 40, 100, and 250 mg/kg/day. **No adverse effects**. NOEL (M/F, systemic) = 250 mg/kg/day based on no effects at the highest dose tested. NOEL (M/F, skin) < 40 mg/kg/day based on epidermal thickening of the treated skin. **Acceptable**. (Corlett, 1/4/01)